

Cardiac toxicity

Danielle Feuvray
UMR CNRS 8078 & Université Paris-Sud XI, France

Correspondence: Professor Danielle Feuvray, CNRS UMR 8078 & Université Paris-Sud XI, Marie Lannelongue Hospital, 92350 Le Plessis Robinson, France.
E-mail: danielle.feuvray@u-psud.fr

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A growing number of studies now demonstrate that alterations in the function of cell membrane transporters, as a result of drug interactions or genetic polymorphisms, may explain a significant portion of efficacy or toxicity in the response to treatment with certain drugs. One prominent example is the variability observed in effects of treatment with digoxin, as discussed in this issue of *Heart and Metabolism* in the article by Lelièvre and Lechat. Fifteen years ago, digoxin, a substrate of the ATP-binding cassette (ABC) transporter known as ABCB1, was shown to be transported by this adenosine triphosphate (ATP)-dependent export pump termed 'P-glycoprotein'. The finding that ABCB1 is expressed in cardiac capillaries and arterioles raised the possibility that the cardiac ABCB1 export pump might prevent accumulation of digoxin in the heart. The article by Couture, Nash and Turgeon provides a concise overview of the role of ABC transporters in distribution of drugs to the heart and protection of the heart from toxic compounds.

Members of the ABC protein superfamily are integral membrane proteins involved in energy-dependent transport of a wide variety of substrates across biological membranes. The most up-to-date information concerning nomenclature of ABC transporters shows that this superfamily is divided into seven different subfamilies (see <http://www.nutrigenet.com/humanabc.htm>; last updated March 2005). Currently, there are approximately 50 functional ABC transporters identified in the human genome, most of which are highly conserved across species.

Many human ABC transporters, such as ABCB1 (P-glycoprotein) or ABCC9 (also known as sulfonyleurea transporter SUR2), are expressed in the heart. It

is of note that mutations in ABCC9, a constituent of cardiac K_{ATP} channels, have been identified in individuals with heart failure and rhythm disturbances. Interestingly, it was reported that the expression of ABC transporters in the heart could be modulated by pathological cardiac conditions. In this respect, a number of recent findings support the idea that expression of ABC transporters in human heart may alter the intracardiac concentrations, and hence the effects, of therapeutic agents and cardiotoxic drugs. Importantly, cardiotoxic effects have been reported that are linked to increased heart drug concentrations after co-administration of antineoplastic agents and agents that reverse multidrug resistance. Thus, in-vitro and in-vivo studies have shown that co-administration of the anthracycline, doxorubicin, a substrate of ABCB1, and of inhibitors of ABCB1, results in an increase in cardiotoxicity.

Cardiotoxicity is, indeed, a well recognized side effect of anthracycline therapy that limits the amount of drug administered and can cause heart failure in some patients. The review by Vergely, Delemasure, Cottin and Rochette points out that the induction of an oxidative stress within myocardial tissue is an important component of anthracycline cardiotoxicity. It also highlights promising strategies aimed at reducing the associated production of reactive oxygen species and consequent cell damage. Furthermore, the Basic Article by Vander Heide provides recent data at the molecular level showing how early anthracycline-induced myocyte DNA damage may be different from the damage induced by a pure oxidative stress, and may represent a novel therapeutic target that may lead to a reduction in cardiac toxicity.